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Authors
Pitre, SP
Muuronen, M
Fishman, DA
et al.

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Tertiary Alcohols as Radical Precursors for the Introduction of Tertiary Substituents into Heteroarenes

Spencer P. Pitre, Mikko Muuronen, Dmitry A. Fishman, and Larry E. Overman*

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

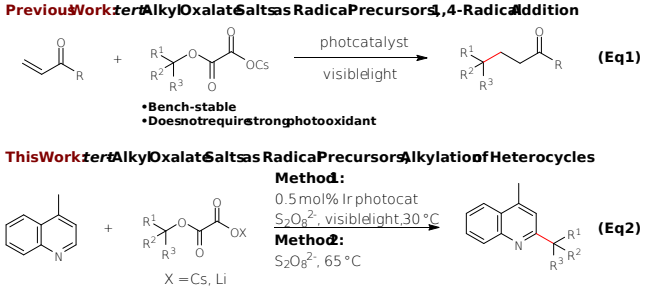
ABSTRACT: Despite many recent advances in the radical alkylation of electron-deficient heteroarenes since the seminal reports by Minisci and coworkers, methods for the direct incorporation of tertiary alkyl substituents into nitrogen heteroarenes are limited. This report describes the use of *tert*-alkyl oxalate salts, derived from tertiary alcohols, to introduce tertiary substituents into a variety of heterocyclic substrates. This reaction has reasonably broad scope, proceeds rapidly under mild conditions, and is initiated by either photochemical or thermal activation. Insights into the underlying mechanism of the higher yielding visible-light initiated process were obtained by flash photolysis studies, whereas computational studies provided insight into the reaction scope.

KEYWORDS: Minisci Reaction, Photoredox Catalysis, Heterocycle Synthesis, C–H Functionalization, Radical Chemistry.

Introduction

The addition of carbon radicals to azines was first reported 125 years ago by Möhlau and Berger.[1] Initial reports in 1968 by Dou and Minisci, and subsequent extensive studies by Minisci, demonstrated that regioselectivities and yields are markedly improved when these reactions are carried out under acidic, oxidizing conditions.[2] The pioneering work by Minisci in this field led to this radical process becoming a fundamental method for C–H functionalization of electron-deficient heteroarenes.[3] The wide functional-group tolerance of radical processes[4] imparts an unusually wide scope to the Minisci reaction, allowing its use for late-stage functionalization of both structurally complex natural products and pharmaceuticals.[3d] The scope and utility of Minisci processes has been greatly expanded in the past decade by the introduction of new precursors and procedures for generating the carbon radical intermediates. The early use of halide and carboxylic acids as radical precursors has been augmented by the recent introduction of boronic acids,[5] sulfinate esters,[6] alkyl trifluoroborates,[7] alkenes,[8] alcohols,[9] *N*-(acyloxy)phthalamides,[10] and 4-substituted dihydropyridines,[11] among others.

In spite of this extensive literature, reports of the functionalization of heteroarenes by the introduction of tertiary carbon substituents and the generation of quaternary centers by Minisci processes are limited.[3] The vast majority of these reports describe only the introduction of adamantyl or *tert*-butyl groups in this fashion.[12] The use of tertiary oxalic acid monoesters as tertiary radical precursors was reported in the early 1990s by Togo and Minisci.[12b,12c,13] In 2015, we and the MacMillan group reported that a wide variety of tertiary radicals can be conveniently generated from *tert*-alkyl oxalate salts using visible-light photoredox catalysis (eq 1).[14] These salts were shown to be excellent precursors of tertiary carbon radicals, as they, in contrast to tertiary half esters of oxalic acid, are quite stable and can be stored for extended periods at room temperature. Another advantage of employing these *tert*-alkyl oxalate salts is that they are significantly easier to oxidize ($\sim E_{1/2}^{ox}$ = +1.22 V vs. SCE) compared to the corresponding oxalic acids ($\sim E_{1/2}^{ox}$ = +1.86 V vs SCE).[15] The mild oxidation potentials of alkyl oxalate salts are well suited for visible-light photoredox catalysis, in particular for the popular iridium heteroleptic photocatalyst, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**I**) [dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4′-di-*t*-Bu-2,2′-bipyridine], which possesses an excited state reduction potential ($E_{1/2}^{red}$) of +1.21 V vs. SCE.[16]

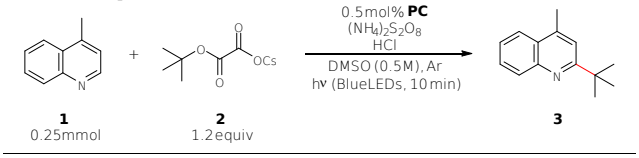


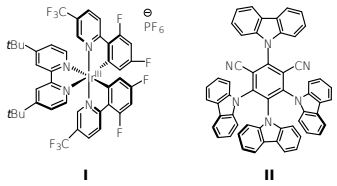
In this report, we present the use of *tert*-alkyl oxalate salts, derived from tertiary alcohols, as radical precursors for the alkylation of electron-deficient heteroarenes (eq 2). The reaction proceeds in good yields with short reaction times, is broad in scope, and the mild oxidation potentials of the *tert*-alkyl oxalate salts enables the reaction to proceed by either photochemical or thermal initiation. Insights into the underlying mechanisms of the transformation are also presented.

Results and Discussion

We first explored the alkylation of lepidine (**1**) with cesium 2-(*tert*-butoxy)-2-oxoacetate (**2**) as the radical precursor. After extensive screening of reaction conditions (See Table S1 of the Supporting Information), it was found that the alkylation of **1** with **2** proceeded in 95% yield within 10 min to generate 2-*tert*-butyl-4-methylquinoline (**3**) employing 0.5 mol % of photocatalyst **I**, 2 equiv of $(NH_4)_2S_2O_8$ as the external oxidant, and 1 equiv of HCl (c = 0.5 M in DMSO) (Table 1, Entry 1). To our surprise, upon removal of the photocatalyst, 94% yield of **3** was still obtained (Entry 2). Although initially puzzling, it was discovered that the observed reactivity was the result of thermal activation, as the reaction proceeded in the absence of light at 65 °C (Entry 3). Owing to the low activation barrier for homolysis of $(NH_4)_2S_2O_8$, the heat generated from the blue LEDs employed in our reaction set-up (~60 °C) was sufficient to cleave the O–O bond,[17] generating two highly oxidizing sulfate radical anions ($SO4^{\bullet-}$).[18] The resulting $SO4^{\bullet-}$ radicals are then capable of oxidizing **2** to generate *tert*-butyl radicals. Interestingly, Minisci and coworkers did not observe reactivity in the absence of $AgNO_3$ in their previous studies with oxalic acid monoesters, likely a result of the higher potential required for oxidation these precursors.[12c] Though we were excited about the observed thermal reactivity, we were also interested in pursuing the reaction under milder, visible-light photoredox catalyzed conditions. It was discovered that the thermal reactivity was attenuated at 30 °C (Entry 4). However, upon irradiation with two Kessil blue LED lamps at 30 °C, we once again observed the formation of **3** in 94% yield (Entry 5). Removal of the photocatalyst under these conditions resulted in formation of only trace amounts of product **3** (Entry 6). Control reactions demonstrated that whereas $(NH_4)_2S_2O_8$ was required for reactivity (Entry 7), the reaction was still viable in the absence of added HCl (Entry 8). Finally, the loading of $(NH_4)_2S_2O_8$ could be dropped to 1.5 equiv, yielding **3** in 94% isolated yield (Entry 9). The reaction can also be performed under air without a significant loss in yield (Entry 10). Seeing as some electron-deficient heteroarenes are prone to oxidative degradation and oxygen is a potent triplet excited-state quencher, it is still recommended to perform these reactions under an inert atmosphere. In addition, we were able to employ the organophotocatalyst 4CzIPN (**II**) in place of Ir photocatalyst **I**, albeit longer reaction times were required to reach comparable yields (Entry 11).

Table 1. Optimization and control reactions for the alkylation of lepidine (1) with oxalate precursor 2.



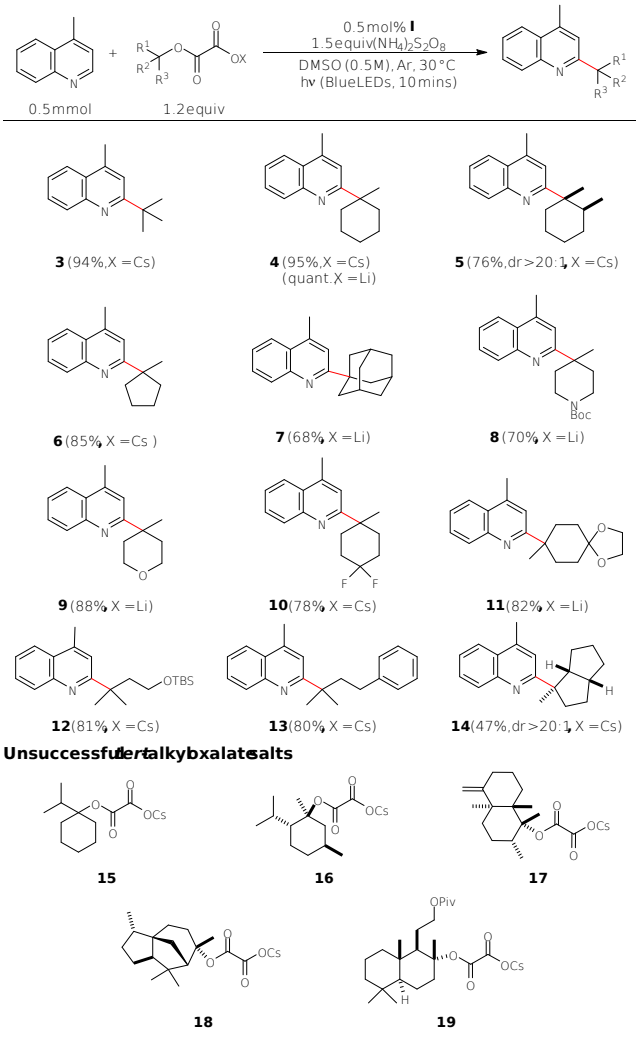


Entry	PC	$(NH_4)_2S_2O_8$	HCl	Conditions	Yield
1	I	2 equiv	1 equiv	hν, 60 °C	95%
2	-	2 equiv	1 equiv	hν, 60 °C	94%
3	-	2 equiv	1 equiv	65 °C	89%
4	-	2 equiv	1 equiv	30 °C	N.R.
5	I	2 equiv	1 equiv	hν, 30 °C	94%
6	-	2 equiv	1 equiv	hν, 30 °C	6%
7	I	-	1 equiv	hν, 30 °C	N.R.
8	I	2 equiv	-	hν, 30 °C	93%
9	I	1.5 equiv	-	hν, 30 °C	94%[a,b]
10	I	1.5 equiv	-	hν, 30 °C	87%[c]
11	II	1.5 equiv	-	hν, 30 °C	96%[b,d]

[a]Reaction was performed at 0.5 mmol scale. [b]yield of isolated purified product. [c]Reaction was performed under air. [d]Reaction was irradiated for 1 h.

With the optimized conditions in hand, we examined the scope of the *tert*-alkyl oxalate salt radical precursors (**Table 2**). As demonstrated in our previous work (eq 1),[14a] the identity of the alkali counterion (Li vs. Cs) had no effect on the reactivity in forming Minisci product **4**. Tertiary radicals derived from 1,2-dimethylcyclohexanol, 1-methylcyclopentanol, and 1-adamantanol added in good yields to give products **5**–**7**. In addition heterocyclic radical precursors provided Minisci products **8** and **9** in high yields. A ketal protecting group was stable under these reaction conditions, presumably because of the absence of exogenous acid which is often required to promote reactivity in Minisci reactions. Acyclic *tert*-alkyl oxalates also provided alkylated products, **13** and **14**, in good yields. Finally, a more complex *cis*-perhydropentalene derivative coupled with **1** in 47% yield with high diastereoselectivity to form **14**, highlighting the utility of this method for installing quaternary centers in complex heteroarenes.[19]

Table 2. Reaction scope of *tert*-alkyl oxalate salts.[a]

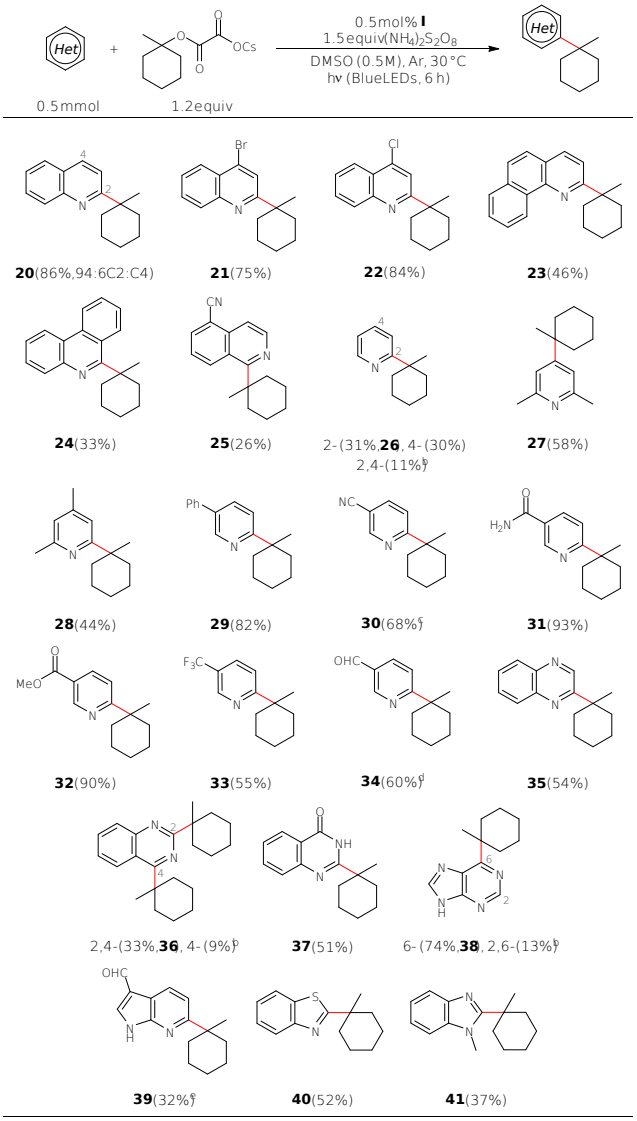


[a]Yields of isolated purified products after 10 min of irradiation using the optimized conditions (see GP1 in the Supporting Information).

In contrast to our previous work on the Giese reaction of tertiary radicals (eq 1),[14a] the Minisci reaction was found to be sensitive to steric hindrance near the radical center. Whereas α- and β-Me groups were well-tolerated (see formation of **5**), an *i*-Pr group at either C1 or C2 of the radical precursor undermined reactivity (oxalates **15** and **16**). Other sterically hindered oxalate salts that were competent coupling partners in the Giese reaction with benzyl acrylate (oxalates **17**-**19**)[14a] did not couple with lepidine (**1**). A computational study determined that the length of the forming C–C bond in the transition state for the addition of *tert*-butyl radical to protonated **1** was 2.14 Å, much shorter than the transition-state bond for the addition of *tert*-butyl radical to methyl acrylate (2.45 Å, see Supporting Information).[20] In addition, the addition of *tert*-butyl radical to protonated **1** was calculated to be slightly endothermic, and potentially reversible. That this step would become more unfavorable with increasing steric encumbrance about the radical carbon is likely responsible for the limited scope of the Minisci reaction of sterically hindered tertiary radicals.

Our survey of the scope of the tertiary Minisci reaction with regard to the heterocyclic component is summarized in **Table 3**. As most heteroarenes reacted more slowly with 1-methylcyclohexyl radical than with lepidine, these reactions were conducted for 6 h. Quinoline yielded the monoalkylated 2-substituted product **20** with 94:6 regioselectivity. High selectivity for introducing tertiary substituents at the 2 position of quinoline was previously reported by Minisci and coworkers, in contrast to the near statistical mixture of C-2 and C-4 regioisomers formed upon reaction with secondary-carbon radicals.[2b] Consistent with these observations, C-2-substituted quinolines were found to be generally unreactive under our reaction conditions. Quinolines harboring halogen substituents at C-4 gave Minisci products **21** and **22** in high yield, whereas 7,8-benzoquinoline and phenanthridine furnished products **23** and **24** in moderate yield. Isoquinolines proved to be much less reactive unless they contained an electron-withdrawing group at C-5, in which case alkylated product **25** was formed in low yield. In contrast to quinoline, pyridine yielded a 1:1 mixture of the 2-(**26**) and 4-alkylated regioisomers, together with 11% of the 2,4-dialkylated product. To our delight, a wide variety of functionalized pyridines gave Minisci products **27**–**34** in good to high yields. Functional groups such as cyano, amides, esters, and trifluoromethyl were tolerated. To no surprise, the alcohol group of 3-pyridinemethanol was oxidized under the Minisci conditions, providing the 3-pyridinecarboxaldehyde adduct **34**. For the majority of the 3-substituted pyridine examples (**29**–**34**), only trace amounts of other regioisomeric products were observed. A variety of other aromatic heterocycles gave Minisci adducts in useful yields. Quinoxaline afforded a single mono-alkylated product **35** in 54% yield, whereas quinazoline gave a 4:1 mixture of the 2,4-dialkylated (**36**) and 4-alkylated products. Quinazolin-4(3*H*)-one provided a single adduct **37** in 51% yield. The 6-alkylated product **38** was formed in 74% from purine together with 13% of the 2,6-di-alkylated product. 3-Formyl-7-azaindole reacted in moderate yield to form **39**. Benzothiazole and 1-methylbenzimidazole were also successfully alkylated, albeit in only moderate efficiency to yield **40** and **41**.[21]

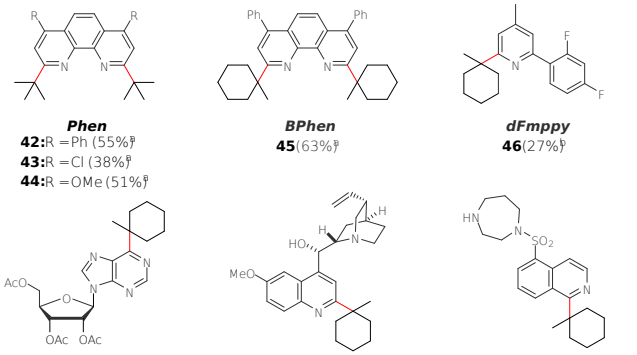
Table 3. Reaction scope of heteroarene.[a]



[a]Yields of isolated purified products after 6 h of irradiation using the optimized conditions (see GP1 in the Supporting Information). Unless noted otherwise, less than 5% of a regioisomeric product was detected by NMR analysis of the crude reaction mixture, or by UV analysis during purification of the crude product. [b]Yield from starting heterocycle. [c]6% of additional regioisomers were detected by ^{1}H NMR analysis of the crude product mixture. [d]From 3-pyridinemethanol. [e]0.4 mmol of the heteroarene and 1.5 equiv of the *tert*-alkyl oxalate salt was employed.

The possibility of introducing *tert*-alkyl substituents into nitrogen ligands commonly employed in organometallic catalysis and biologically relevant heteroarenes was of particular interest (**Table 4**). Using 2.4 equiv of the oxalate salt, 4,7-disubstituted phenanthrolines and bathophenanthroline were dialkylated in useful yields to give the sterically hindered phenanthroline ligands **42**–**45**. The ease of this method for the functionalization of phenanthrolines should allow for streamlined preparation of a variety of sterically hindered phenanthroline ligands, including ones that incorporate chiral, enantiopure tertiary substituents. As one additional example, 2-(2,4-difluorophenyl)-4-methylpyridine was alkylated to give the sterically hindered dFmppy ligand analogue **46**. Purine riboside (**47**), quinine (**48**), and the rho-kinase inhibitor and vasodilator fasudil (**49**) were also alkylated to incorporate 1-methylcyclohexyl substituents in good to moderate yield. The yield of the fasudil analogue **49** could be increased to 39% by using 3 equiv of the oxalate salt precursor.

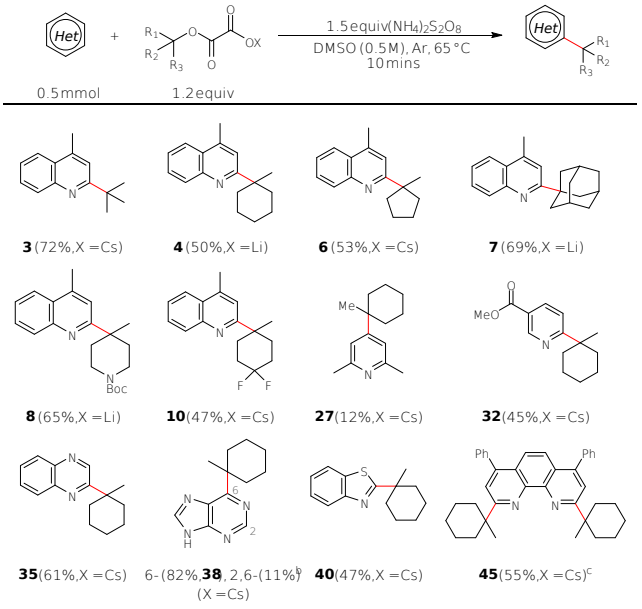
Table 4. Reaction scope of the alkylation of ligands and biologically-relevant heteroarenes.



[a]Modified Conditions: ligand (0.25 mmol), *tert*-alkyl oxalate (2.4 equiv), PC **I** (1 mol %), and $(NH_4)_2S_2O_8$ (3 equiv) in 1 mL of DMSO were irradiated for 6 h using two Kessil blue LED lamps at 30 °C under Ar. Yields of isolated purified product. [b]Yields of isolated purified products after 6 h of irradiation using the optimized conditions (see GP1 in the Supporting Information).

Finally, the scope of the thermally-initiated Minisci reaction was briefly examined (**Table 5**). Under the conditions employed, the tertiary radical precursor was completely consumed within 10 min at 65 °C. In six of the examples (synthesis of **3**, **4**, **6**, **10**, **27**, **32**), the yield of the thermal reaction was significantly lower (30–45%) than that realized under visible-light photoredox conditions. It should be noted that unreacted heteroarene is typically recovered in these cases, therefore higher yields undoubtedly could be achieved by employing an excess of the oxalate salt and $(NH_4)_2S_2O_8$. In the remaining examples (synthesis of **7**, **8**, **35**, **38**, **40**, **45**), the yield was comparable under thermal and photochemical conditions. In spite of the lower yields sometimes observed, the thermal reaction should be easier to implement and attractive for the parallel synthesis of a large collection of analog structures.

Table 5. Reaction scope of the thermal Minisci reaction.[a]



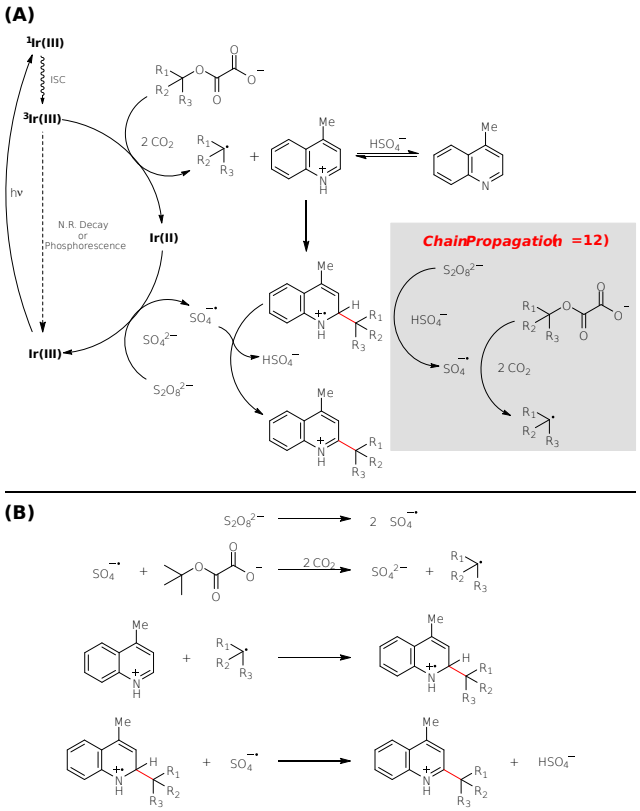
[a]Yields of isolated purified products after 10 min at 65 °C using the optimized conditions (see GP2 in the Supporting Information). [b]Yield from purine. [b]0.25 mmol of BPhen was used.

In order to rationalize the high efficiency of the photoredox-catalyzed Minisci reaction, we turned to excited state kinetic analysis using laser flash photolysis techniques. The pseudo-first-order rate constant (k_{obs}) for the excited state decay was monitored using the luminescence of **I**, and the bimolecular rate constant (k_q) was obtained from a plot of k_{obs} versus the concentration of the quencher (See section IJ of the Supporting Information).[22] As expected, the excited state of the photocatalyst (***I**) is not quenched by $(NH_4)_2S_2O_8$; however, both lithium 2-((1-methylcyclohexyl)oxy)-2-oxoacetate and **1** are efficient quenchers of ***I** (3.29×10^8 and 1.29×10^8 $M^{-1}s^{-1}$, respectively). At first glance, it would seem that quenching by **1** would result in significant reaction inhibition, as the desired outcome involves oxidative quenching by the *tert*-alkyl oxalate salt. However, a more accurate comparison would be the fraction of triplets quenched after accounting for the concentrations of each reagent under initial reaction conditions. The fraction of triplets quenched can be easily calculated using eq 3;[23]

$$\%\,{}^*\mathrm{I}\ \mathrm{Quenched} = \frac{100\% \times k_q^{\square}[\mathrm{Quencher}]}{\tau_0^{-1} + k_q^{\mathrm{Lepidine}}[\mathrm{Lepidine}] + k_q^{\mathrm{Oxalate}}[\mathrm{Oxalate}] + k_q^{\mathrm{F}}} \quad \text{(Eq 3)}$$

where the various k_q terms refer to the aforementioned bimolecular rate constants, and τ_0 refers to the lifetime of ***I** in the absence of a quencher (1.1 μs). Under our standard reaction conditions, we calculate that the fraction of ***I** being quenched by lithium 2-((1-methylcyclohexyl)oxy)-2-oxoacetate is actually 75%, while quenching by **1** only accounts for 25%. Furthermore, chemical actinometry experiments revealed a quantum yield of 12 (See section JK of the Supporting Information),[24] indicating significant chain propagation. A synergistic combination of efficient excited state quenching and high quantum yield likely accounts for the unusually short reaction times observed.

The proposed mechanism for this transformation is outlined in Scheme 1A. Upon excitation with blue LEDs, ***I** is oxidatively quenched by the *tert*-alkyl oxalate, triggering a double decarboxylation to form a tertiary radical. The radical then adds to the protonated heteroarene, yielding an amine radical-cation intermediate. This intermediate then undergoes a proton-coupled electron-transfer with $SO4^{\bullet-}$, generated by the reductive cleavage of $(NH_4)_2S_2O_8$ in the catalyst turn-over step, to yield the final product and HSO_4^-. We propose that the amine radical-cation intermediate can also be quenched by $(NH_4)_2S_2O_8$ to yield HSO_4^- and $SO4^{\bullet-}$, the latter of which can initiate chain propagation by oxidizing the *tert*-alkyl oxalate salt. The likely mechanism of the thermal Minisci reaction is outlined in Scheme 1B.



Scheme 1. Proposed mechanisms for the photoredox-catalyzed Minisci reaction (A)

and the thermally initiated Minisci reaction (B) of *tert*-alkyl oxalate salts.

Conclusion

An attractive method for appending *tert*-alkyl substituents to electron-deficient heteroarenes by either photochemical or thermal initiation has been developed. The more efficient visible-light promoted reaction is accomplished within minutes or hours at 30 °C and employs only 0.5 mol % of an Ir photocatalyst. The mild conditions and short reaction times of this Minisci reaction result from a synergistic combination of efficient excited state quenching of the photocatalyst and chain propagation.

AUTHOR INFORMATION

Corresponding Author

*leoverma@uci.edu

Present Addresses

M.M.: BASF SE, Carl-Bosch-Strasse 38, 67056 Ludwigshafen,
Germany.

ASSOCIATED CONTENT

Supporting Information. The supporting information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, reaction optimization, laser flash photolysis data, quantum yield experiments, compound characterization, and NMR spectra.

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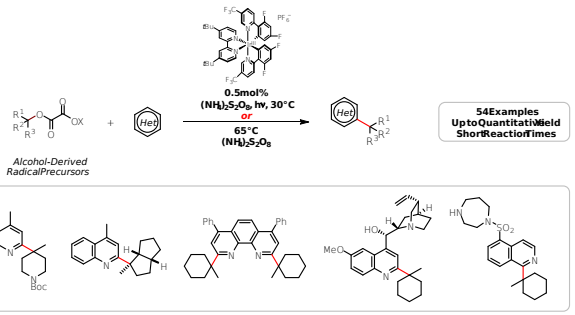
0.5mol%
(NH4)2S2O8, hv, 30°C
or
65°C
(NH4)2S2O8
Het
Alcohol-Derived
RadicalPrecursors
54Examples
UptoQuantitativeYield
ShortReactionTimes